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AUTHOR(S):

MORIYASU, HISASHI

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THE LOWER BRAIN STEM AND CONSCIOUSNESS

By

Hisashi Moriyasu

From the 1st Surgical Division, Kyoto University Medical School
(Director Prof. Dr. Chisato Araki)
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SECTION I

NICOTINE-COMA INDUCED FROM THE LOWER BRAIN STEM AND THE EFFECT OF THE RECTANGULAR PULSE STIMULATION OF THE LOWER BRAIN STEM *

Concerning the relation between the lower brain stem and consciousness, it has been found long since that unconsciousness occurs in the operation of the posterior fossa more frequently than in that of any other locus of the brain, but comparatively few studies have ever proved this fact by experiment (Breslauer). It is only lately that Magoun's theory of the ascending reticular activating system has elucidated the function in consciousness mechanism of the reticular system of the brain stem including the lower brain stem.

Some years ago, we met with a patient of probable pontine or "reticular" epilepsy, which had some connection with this problem. A twenty-eight-year-old man had commotio cerebri a year and a half ago, and at times since then he had epileptic fits, which caused first the loss of consciousness and next the convulsions of the right half of the body. Neurologically, we noticed a crossed hemihypesthesia. Pain, thermal and tactile sensibilities were reduced in the right upper and lower extremities and in the left half of the face, and there was motor paresis in the right half of the body except the face. The findings led us to guess that there might be a traumatic disorder in the left half of the pons. The fit could be caused instantly by pain stimuli given to any part of the body. First there came the loss of consciousness; about ten seconds later tonic convulsions of the right upper and lower limbs; then clonic convulsions or twitchings; and the fit died away. After an intravenous anaesthesia of Ravonal (thiopental sodium) the patient had stronger convulsions. The electroencephalogram during the fit showed low voltage fast waves both in the period of coma and in the period of convulsions, and never showed slow waves. After all, in this case, the epileptic focus was supposed to be probably near the reticular formation of the caudal part of the pons, the abnormal excitement of which caused an arousal reaction in electroencephalogram and coma in behavior.

Thus it seems that there can be a disturbance in consciousness in case of a

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disorder of the lower brain stem. The aim of the present study lies in proving it in ananimal experiment.

Now, what is most difficult in an experiment of this kind is how to judge objectively the consciousness of animals. In animals that can not answer in words whatever, we have no means of judging it except to use as a mark their behavioral reaction or their noci-reflex. Therefore, we classify the stages of the disturbance of consciousness in animals as follows, based on the symptoms of a cat when it is anaesthetized by ether or barbiturate.

I) Unresponsiveness I (semi-coma I)

In this stage, spontaneous movements disappear. The postural reflex becomes rather sluggish; and the reaction to light and sound as well as the escape-movement caused by the tactile stimuli upon the surface of the body are lost for the most part, but the reaction to pain and olfactory stimuli remains clearly. (Girndt II--IV)

II) Unresponsiveness II (semi-coma II)

In this stage, spontaneous movements and the postural reflex disappear completely. The olfactory reflex is lost, too, to say nothing of the reflexes caused by optic, acoustic, and tactile stimuli. The noci-reflex from the surface of the body is weakened, but remains a little. The sneezing reflex from the nasal septum, the noci-reflex to the nose, and the pharyngeal reflex all remain. (Girndt IV--V)

III) Unresponsiveness III (coma)

In this stage, the noci-reflex to the nasal septum and the nose, and the pharyngeal reflex are all lost; but the corneal reflex, the pupillary reaction to light, and the reflex to the pain stimuli in the ears may remain. The patellar reflex may remain or may not. (Girndt V--)

The spontaneous movements that we have examined here are blinking, vocation, lick of the chips, chewing, swallowing, and movements of the ears, the head, the limbs, and the tail.

Method

A cat of 2 or 3 kg in weight is fixed on a hammock and is allowed to let the extremities hang down naturally. Then, under ether anaesthesia, trephination is performed as small as possible in the parietal or suboccipital region. When ether effect is gone completely, the cat is punctured with a needle, 1/4 mm in size, 12 cm in length reaching a certain locus in the lower brain stem from the trephination opening under the guidance of the HORSLEY-CLARKE's stereotaxic instrument, which is previously placed on the head of the cat. And then the cat is given an injection of pure nicotine or a solution of nicotine diluted twice as weak by a methyl cellulose solution. And according to the abovesaid criteria, the change of responsiveness is examined twice, once after the puncture of the needle and once again after the injection of nicotine. When the injection is given twice in two places in the same cat, the second one is to be given when the cat has returned to normal after the interval of over three hours.

And in order to compare with this nicotine experiment, the change of responsiveness is examined, by stimulating the animal at nearly the same area by rectangular pulses. To be precise, by stimulating with 1 msec. rectangular pulses, after the insertion of a 12-cm-long bipolar electrode, which had a diameter of 0.5 mm and is insulated except about 0.3 mm at the tip, the change of responsiveness and behavior is examined according to the above-said criteria. The condition of the stimulation is 3, 10, 30, 60 and 100 cycles, and 1, 2, 4 and 8 volts respectively. Ten volt direct current is applied for 7 seconds to mark the stimulated locus for the purpose of histological examination. The brain is fixed with pure alcohol, embedded in celloidin and is cut into 30-μ-serial sections, and the stimulated loci were ascertained by Nissl stain and myelin sheath stain in the case of nicotinization and by ironcarmine stain besides them in the case of the electrolytic foci.

Results

A. Experiments with pure nicotine

In 35 survivals we could observe the state of consciousness. Injection was performed in 48 loci.

1) Mesencephalon Groups

In the cats which had a lesion in the central grey matter at the level between the oculomotor and trochlear nuclei and in the adjacent reticular formation, i. e. the locations which had been pointed out by Yabuno before, two out of five (Nos. 38, 39, 42, 68, 69) fell into unresponsiveness II and III, No. 38 (Fig. 1) for about 10 minutes, and No. 39 (Fig. 2) for about 4 minutes respectively.

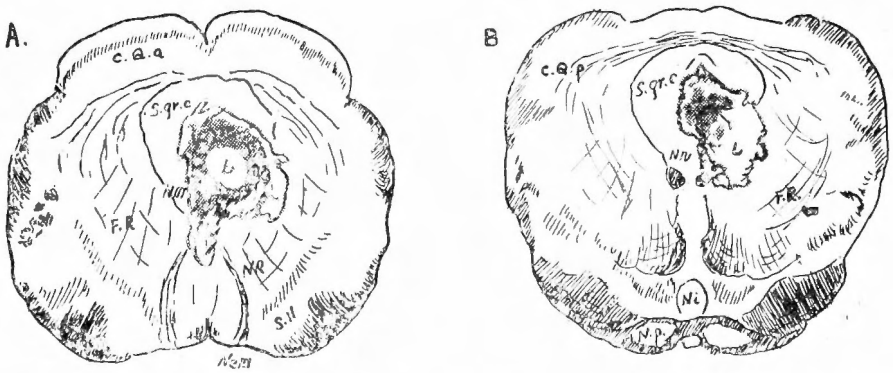


Fig. 1 Transverse sections through the midbrain (A) and pons (B) of No. 38 cat. (coma) Abbreviations are as follows: C. Q. a., C. Q. p.; corpus quadrigeminum ant. post., F. R.;formatio reticularis, L: lesion, N. Ⅲ, Ⅳ; nucleus oculomotorius, trochlearis, Ne. Ⅲ; nervus oculomotorius, N. R.; nucleus ruber, N. i.; nucleus interpeduncularis, N. p.; nucleus pontis, S. gr. c.; substantia grisea centralis, S. N.; substanttia nigra.

The Cat No. 38 (♀, 2.6 kg): mews and behaves violently before the puncture. The nocireflex is normal. No change due to the mere puncture with the needle is observable. It mews and moves its forelimbs feebly even after the injection of nicotine. Twenty-five seconds later, the cat becomes completely quiet, and ceases to mew. Only respiration accelerates. The pupils dilate moderately. The pupillary reaction to light is lost. The corneal reflex is weakened. The

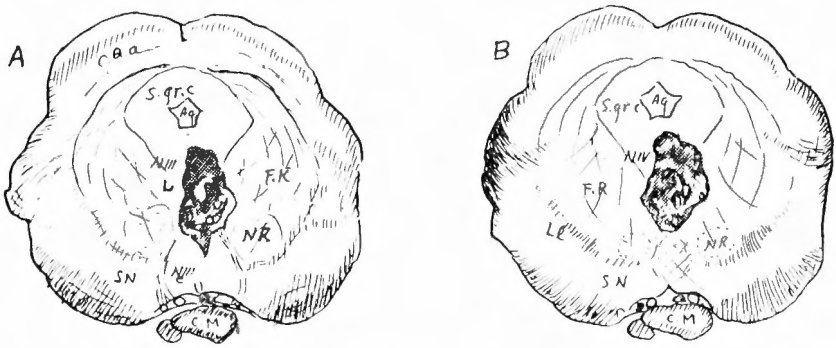


Fig. 2 Transverse sections through the midbrain at the level of nucleus oculomotorius (A) and nucleus trochlearis (B) of No. 39 cat. (coma)

noci-reflex and the tonus of the muscles are lost (coma). Three minutes and a half later, the ears begin to respond to painful stimuli. Four minutes later, the sneeze reflex due to the stimulation of the nasal septum and the pharyngeal reflex are recovered slightly. The pupils dilate moderately and the corneal reflex is recovered, but the noci-reflex is still lost. The tonus of the muscles somewhat recovers. Six minutes later, the pharyngeal reflex and the tonus of the muscles become normal (semicoma II). Ten minutes later, the cat licks the chips if it is given a pharyngeal stimulation (recovery). Twelve minutes later, the cat begins to mew at intervals and behave violently. The pupillary reaction to light, the corneal and the noci-reflexes become normal.

In two cases (Nos. 35, 41), injection was given to the mesencephalic reticular formation, but unresponsiveness did not occur at all.

2) Pons Groups

In one case (No. 57) (Fig. 3), in which the center of the lesion was in the floor grey matter of the fourth ventricle at the rostral level of the pons and in its adjacent reticular formation, but the rostral end of the lesion was close to the wall of the aqueduct, unresponsiveness II was observed for about 11 minutes.

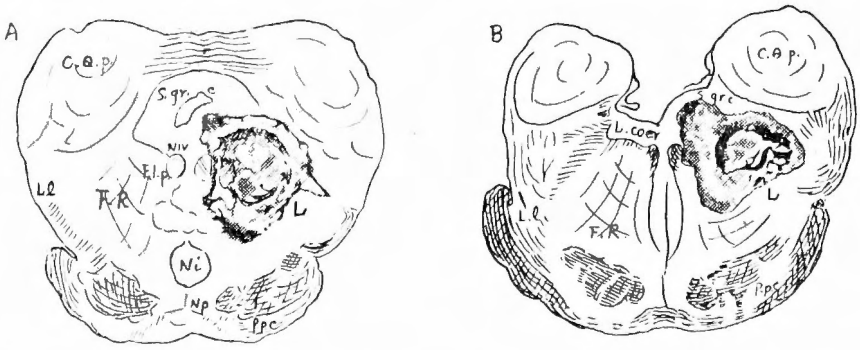


Fig. 3 Transverse sections through the pons at the level of rostral (A) and caudal (B) end of No. 57 cat. (semicoma) Abbreviations are as follows; F. l. p; fasciculus longitudinalis post., L. coer.; locus coeruleus, L. l.; lemniscus lateralis, P. p. c.; pes peduaculi cerebri.

The Cat No. 57 (♀, 2.8 kg): mews and behaves violently before the puncture. The noci-reflex is normal. No change due to the mere puncture with the needle is observable. Simultaneously with the injection, mewing and spontaneous movement cease. One minute later,

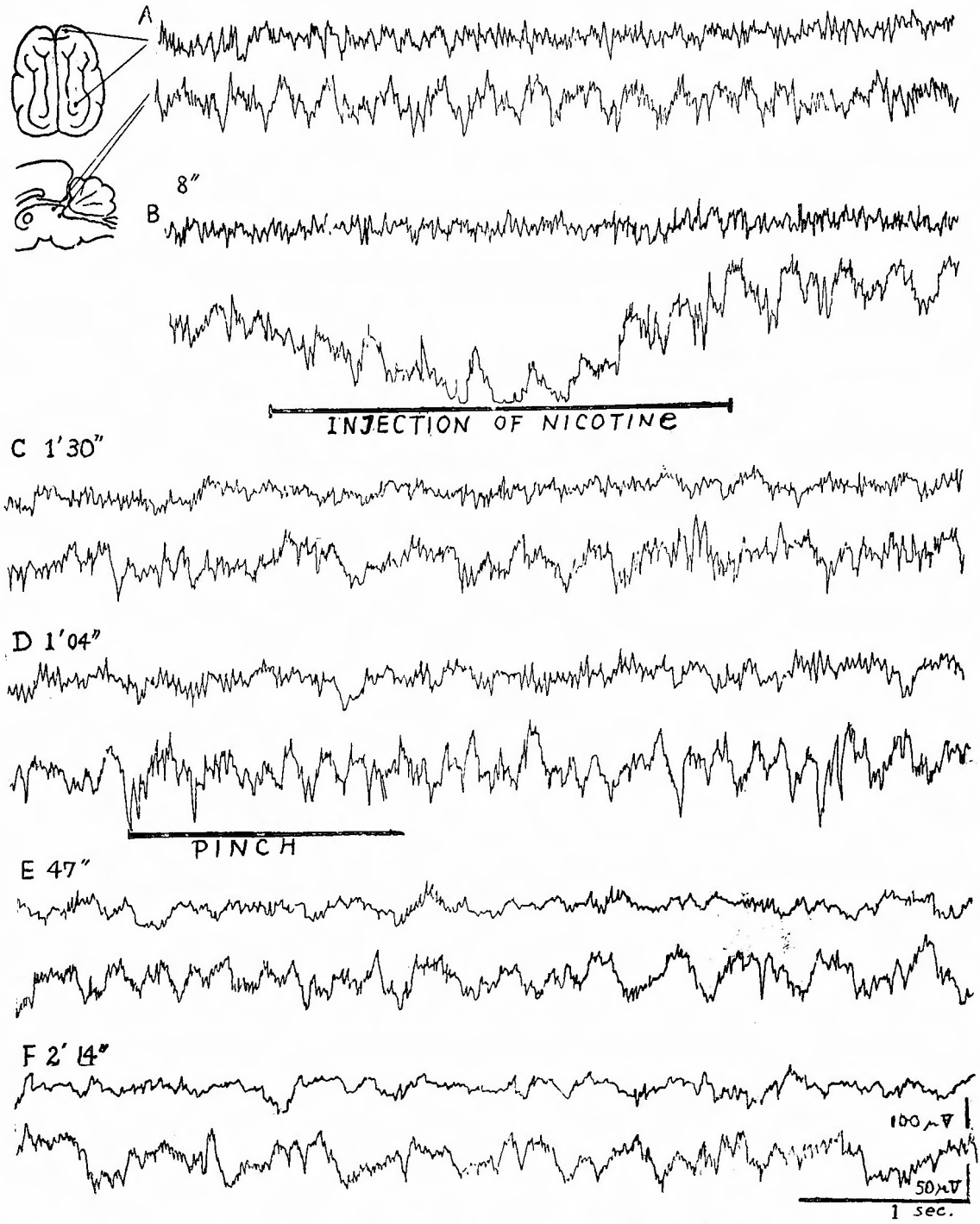


Fig. 4 Serial electroencephalographic tracings in cat No. 57, in which the lesion involved the rostral pontine grey matter. All records characterized by low-voltage fast activity and no change is found by painfull stimuli. Upper beams are recorded from cortex and lower beams from adjacent portion of lesion. (A) before and (B) during injection (C) (D) (E) semicoma (F) waking

gasping begins and the pupils dilate moderately. The tonus of the muscles is lost. One minute and twenty seconds later, a slight reflex to the stimulation of the nasal septum and the pharynx is observable; but the other noci-reflexes and the corneal reflex are all lost and the complete stillness continues (semi-coma II). Two minutes and a half later, the pupils dilate slightly, and the reflex to the olfactory stimuli is slightly present; but the noci-reflex is utterly lost. Three minutes and a half later, the right corneal reflex is recovered a little. Then the cat vomits. Six minutes later, the tonus of the muscles somewhat recovers. Nine minutes later, the reflex to the olfactory stimuli and the painful stimulation of the ears come back. Eleven minutes later, the twitching of the ears begins and the noci-reflex is recovered almost completely (recovery). Fifteen minutes later, the corneal reflex comes back. Twenty minutes later, the pharyngeal reflex comes back. Thirtyfour minutes later, spontaneous movement can be observed again.

In this case, the electroencephalogram during semi-coma (Fig. 4) shows fast waves (but of somewhat low voltage) (30 to 50μ V, 30 to 50 c/s), much the same as before the injection; and slow wave element or spindle burst, etc. are not observable. Besides, it shows no change even when the painful stimuli are given.

In those four cases [Nos. 1, 60, 64 (Fig. 5. A), 67] when the nicotine, which was injected in the floor grey matter on the borders of the pons and medulla (locus coeruleus), reached the tegmental reticular formation, and in another seven cases [Nos. 37 (Fig. 5. B), 38, 42, 44, 71, 73, 75], when nicotine was injected in the pontine reticular formation, unresponsiveness did not occur at all. Besides, in the six cases among them (Nos. 37, 64, 67, 72, 73, 75) we could observe running

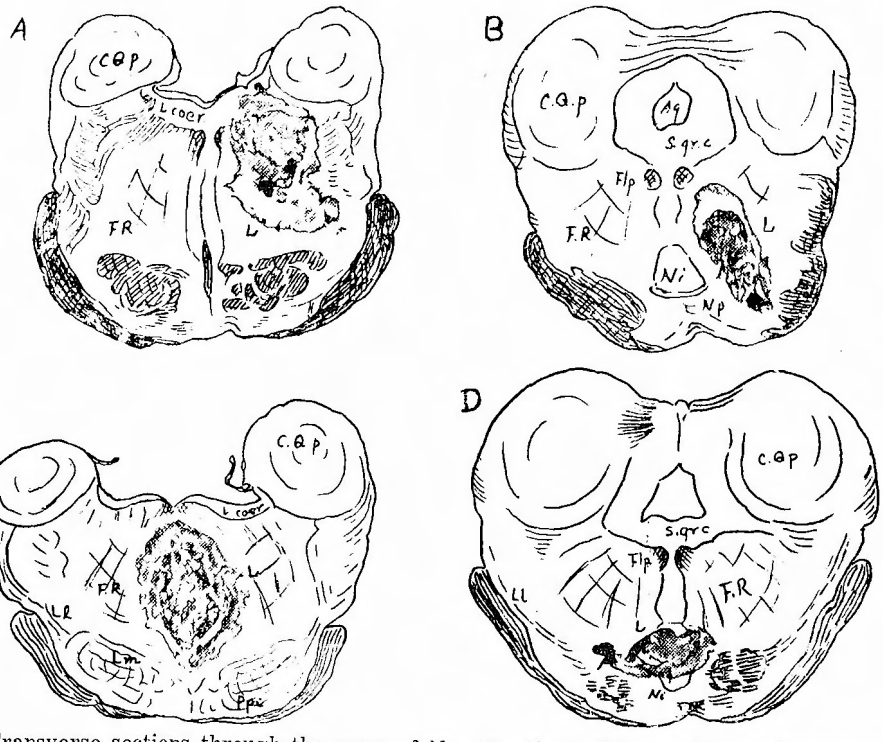


Fig. 5 Transverse sections through the pons of No. 64 (A), 37 (B), 72 (C) cat. (no disturbances inconsciousness) and of No. 41 cat (D). (coma)

movement, and in the two (Nos. 38, 60), exaggeration of excitability.

In the three cases (Nos. 4, 69, 70), too, when injection was given in one side of the nuclei pontis, unresponsiveness did not occur. Only in one case (No. 41) (Fig. 5. D) out of the two (Nos. 39, 41), when injection was given in the caudal part of the nucleus interpeduncularis, unresponsiveness II and III lasted for about 7 minutes; but to cause coma after the injection about three minutes were required in striking contrast to the short time such as 30 seconds to 1 minute required in those cases so far dealt with.

The Cat No. 41 (♀, 2.7 kg) : mews loudly and keeps struggling before the puncture. The noci-reflex is brisk. When the needle is inserted, it mews and behaves violently, and even after injection keeps mewing and struggles a little. One minute and a half later, the cat mews feebly but spontaneous movement ceases. Respiration accelerates, and the right pupil dilates moderately. but the noci-reflex is normal. Three minutes later, it stops mewing and keeps still. Myosis occurs. The reaction to light, the pharyngeal and the noci-reflexes, and the tonus of the muscles are all lost. The corneal reflex becomes weakened (coma). Six minutes later, the tonus of the muscles in the right forelimb returns. Nine minutes later, the pharyngeal reflex and the noci-reflex to the ears, the nasal septum, and the tip of the nose are recovered slightly; and the tonus of the muscles becomes nearly normal (semi-coma Ⅱ). Ten minutes later, spontaneous movement in the left forelimb appears, but mewing does not come back yet. The noci-reflex is almost normal (recovery). Fifteen minutes later, the cat begins to lick the chips. Twenty-seven minutes later, it begins to mew loudly and struggle.

3) Medulla Groups

For convenience' sake, the medulla is divided into three parts. The rostral part is from the level of decussatio lemnisci, nucleus nervi trigemini, and nucleus olivaris superior to the appearance of the root fibers of nervus abducens and facialis (E to F in Fig. 12). The middle part denotes the area including nucleus vestibularis and facialis (G to I in Fig. 12.). The caudal part is from the level of nucleus vagus, nucleus olivaris inferior and the root fibers of nervus hypoglossus to decussatio pyramidalis (K to M in Fig. 12).

In the rostral part group, No. 46 (Fig. 6. A), which had injection in the tegmental reticular formation, showed unresponsiveness II and III for about two

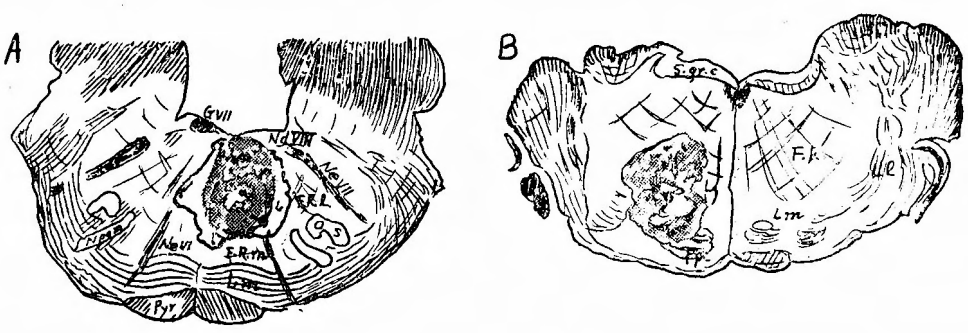


Fig. 6 Transverse sections at the rostral bulbar level of No. 46 cat (A) and No. 74 cat. (coma) Abbreviations are as follows : F. R. l. et m.; formatio reticularis lateralis et medialis, G. Ⅶ; genu nervi facialis, N. d. Ⅷ; nervus dorsalis nervi octavi, N. p. o. m.; nucleus parolivaris sup. med., Ne. Ⅵ et Ⅶ; nervus abducens et facialis, Pyr; tractus pyramidalis, O. s.; nucleus olivaris superior.

minutes, and No. 74 (Fig. 6. B) of the four cases (Nos. 21, 69, 73, 74), which had injection in the ventromedial part of the reticular formation (nucleus papillioformis), showed unresponsiveness II and III for about eight minutes and a half.

The Cat No. 46 (♀, 1.9 kg) : continues mewing before the puncture and spontaneous movement is very active. No change due to the mere puncture is visible. Immediately after the injection, no remarkable change except the dilation of pupils is visible. One minute later, respiration accelerates and the cat stops mewing but struggles with its limbs. The corneal reflex and the pharyngeal reflex are weakened strikingly. One minute and forty-five seconds later, it is still reactive to tactile stimuli. Two minutes later it becomes completely still, and the reflexes to olfactory and tactile stimuli the noci-reflex except in the ears, the pharyngeal reflex, and the tonus of the muscles all disappear (coma). Three minutes later, the tonus of the muscles in the right foreleg is recovered slightly. Four minutes and a half later respiration is still accelerated, and the cat sometimes begins to struggle with the foregs. The tactile and the pharyngeal reflexes are recovered, and the corneal reflex is provable though sluggish (awakening). Sex minutes later respiration becomes calm, myosis is observed, and the corneal and the noci-reflexes and the tonus of the muscles are all normal. Eight minutes and forty seconds later, the cat mews again and spontaneous movement becomes active.

The Cat No. 74 (♂, 2.2 kg) : mews and struggles violently before the puncture, and the noci-reflex is normal, and licks the chips when pharyngeal stimuli are given. It becomes a little calmer after the mere puncture. Immediately after injection the cat is in rage and continues to mew. Thirty seconds later respiration accelerates, and the cat stops both mewing and struggling and becomes quite still. Urinary incontinency is observed, and the noci- and the pharyngeal reflexes disappear and only the left corneal reflex remains (coma). One munute later the cat mews feebly. No reflex to the olfactory stimuli is observed, and only the noci-reflex in the nose is provable (semi-coma). Two minutes later the tonus of the muscles disappears. Three minutes later the cat shows the twitching of the ears. Four minutes later the corneal and the pharyngeal reflexes are recovered, and the cat licks the chips when pharyngeal stimuli are given. Four minutes and a half later, the tonus of the muscles is recovered slightly. Six minutes later the cat blinks spasmodically. Eight minutes later the spasmodic movement of the forelegs is observed once. Nine minutes later the olfactory and the noci-reflexes are recovered (recovery). Fourteen minutes later it mews and struggles violently, and bites and licks the chips. The noci-and the postural reflexes are recovered.

In the middle part group, the Cat No. 45 (Fig. 7. A) of the two cases (Nos. 45, 81), which were given injection in the floor grey matter (nucleus vestibularis), ceased to move instantly after injection and seemed unresponsive; but spontaneous movements and the noci-reflex became active rapidly 30 seconds after. The four

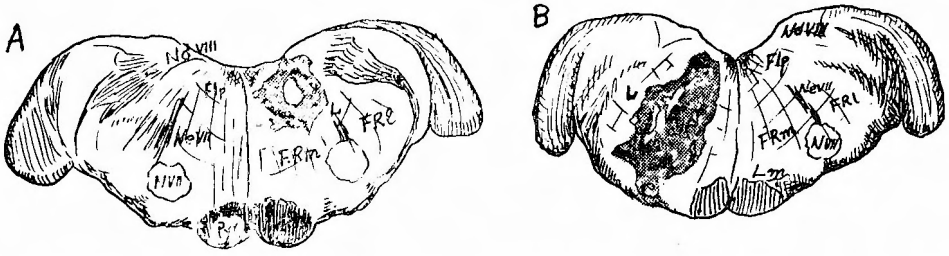


Fig. 7 Transverse sections at the middle bulbar level of No. 45 cat (A) (momentary coma) and No. 80 cat (no disturbances in consciousness). Abbreviations are as follows : N. Ⅶ; nucleus facialis, N. d. Ⅲ; nucleus dorsalis nervi octavi.

cases [Nos. 16, 48, 68, 80 (Fig. 7. B)] which were given injection in the reticular formation did not show unresponsiveness.

In the caudal part group, No. 47 (Fig. 8. A), which had injection in the floor grey matter (nucleus vagus, hypoglossus), did not show unresponsiveness; but No. 2 stopped moving simultaneously with the mere puncture, and unresponsiveness lasted for about three minutes.

Out of the five cases (Nos. 12, 17, 59, 60, 61) which had the lesion in the unilateral medial and lateral reticular formation, one case (No. 12, Fig. 8. B) showed unresponsiveness III for two minutes and a half; and out of the three cases (Nos. 14, 20, 63) which had the lesion in the bilateral medial reticular formation, two cases showed unresponsiveness II and III. In No. 14 (Fig. 8. C), the lst puncture (L. 1) in which injection was given in the medial reticular formation resulted in unresponsiveness II and III for about five minutes and a half, while the 2nd puncture (L. 2) in which injection was given in the lateral reticular formation caused no unresponsiveness; and No. 63 (Fig. 8. D) showed unresponsiveness II and III for about three minutes.

It is noteworthy that in all these bulbar cases showing coma respiratory movement became as much quick as in the mesencephalic or the pontine groups but any particular dyspnoea or apnoea was not accompanied, although bulbar nicotine injection was apt to cause respiratory stop in other cases.

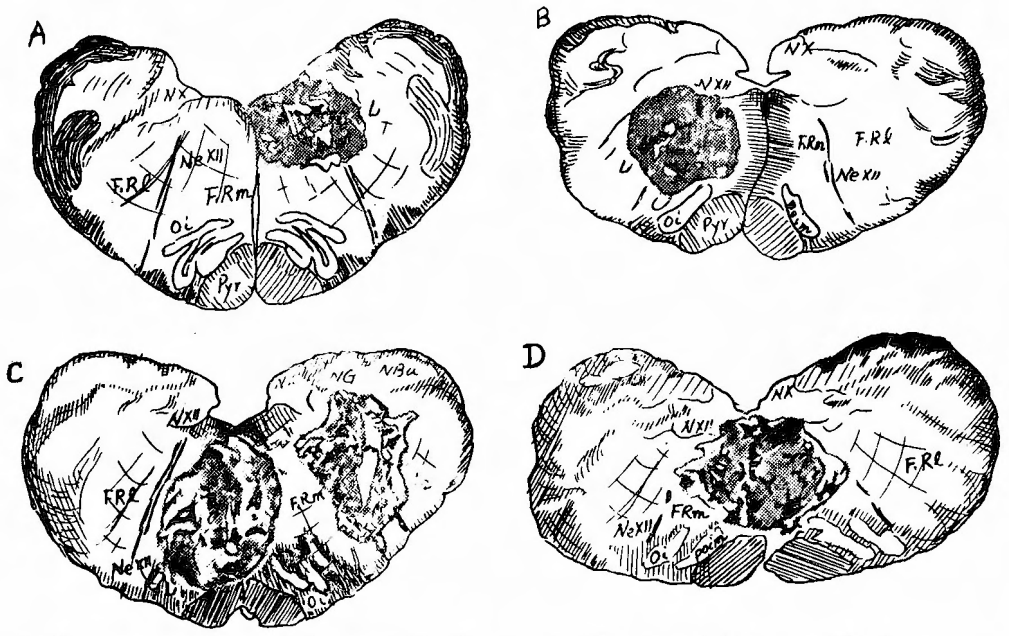


Fig. 8 Transverse sections at the caudal bulbar level of No. 47 cat (A). (no disturbances in consciousness) and of No. 12 (B), 14 (C) (L_1 : lesion in the medial reticular formation; coma, L_2: lesion in the lateral reticular formation; no disturbances in consciousness.) and 63 (D) cat. (coma) Abbreviations are as follows : N. G.; nucleus Goll, N. Bu.; nucleus Burdach, N. X; nucleus vagus, N. XII; nucleus hypoglossus, Ne. XII; nervus hypoglossus, O. i.: nucleus olivaris inf., P. o. i. m.; nucleus parolivaris inf. med.

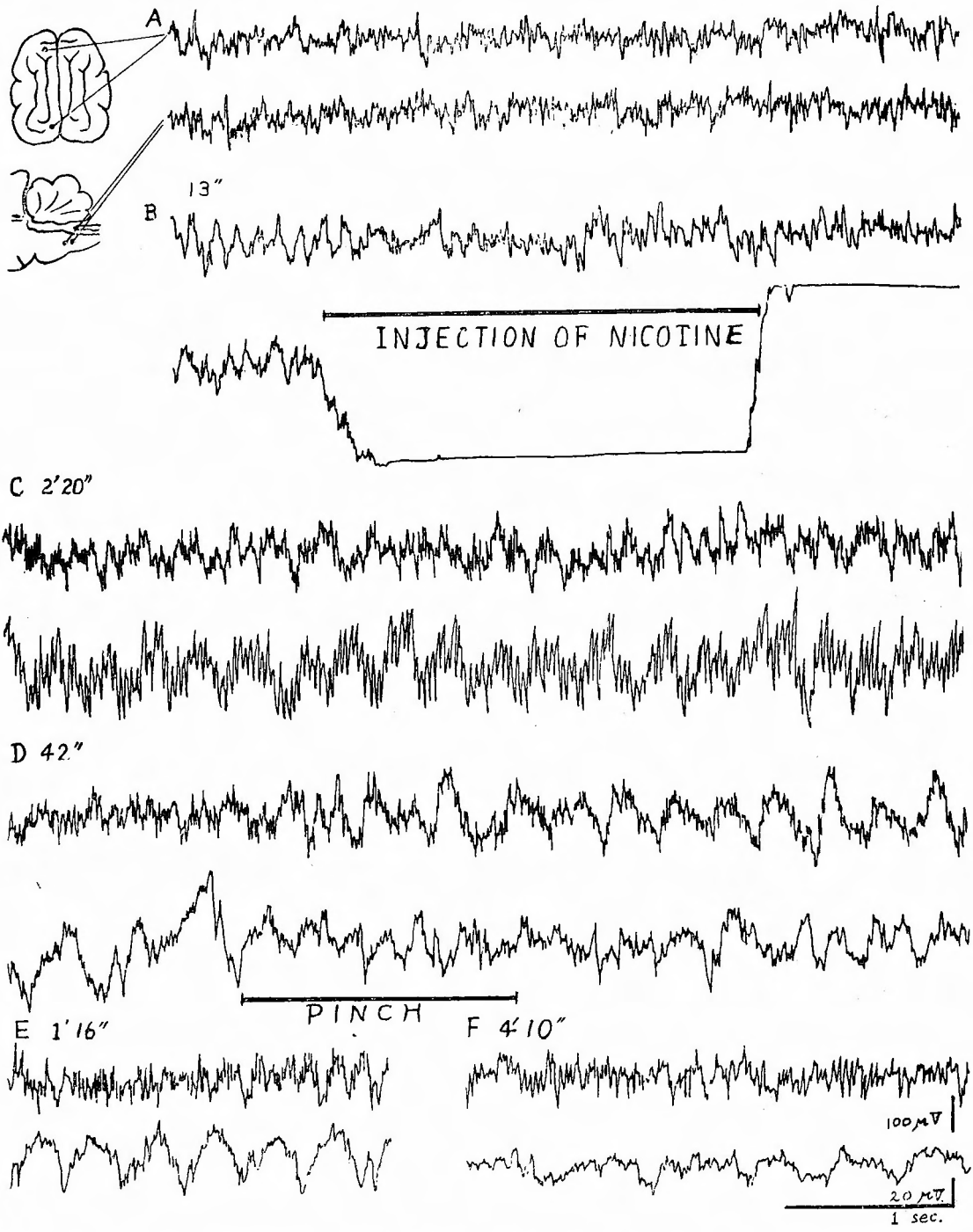


Fig. 9 Electroencephalographic recordings from cat No. 63, in which the lesion involved the medial bulbar reticular formation. Note persistent low-voltage fast activity in all tracings, absence of response to painfull stimuli. Upper beams are recorded from cortex and lower beams from adjacent portion of lesion. (A) before and (B) during injection. (C) (D) (E) coma. (F) waking.

The Cat No. 63 (♂. 2.8 kg) : mews and struggles violently and licks the chips before the puncture. No change due to the mere puncture is observed. The noci-reflex is normal. The cat rages after injection. Twenty five seconds later respiration accelerates and the pharyngeal reflex disappears. A minute later it still moves its forelimbs violently and the noci-reflex is normal. Two minutes later spontaneous movement and mewing stp, and it becomes still. The reaction to olfactory and tactile stimulation and the noci-reflex are all lost. The tonus of the muscles is weakened and the corneal reflex is retained a little but is sluggish (coma). Even four minutes later it is still commpletely quiet. The pupils are dilated moderately. Five minutes later the noci-reflex is nearly recovered, but the pharyngeal and the corneal reflexes are weakened (recovery). Seven minutes and a half later the cat begins to struggle with its forelimbs. Eight minutes and a half later the pharyngeal reflex becomes normal and the cat begins to bite and lick the chips.

As for the electroencephalographic tracings during the coma of No. 63, both surface and deep E. E. G. s were low voltage fast waves (10 to 50μ V, 30 to 60 c/s) and showed no change by painful stimuli.

In the more caudal level group, all the three cases (Nos. 17, 18, 58) which had injection in the medullary central grey matter and the reticular formation did not show any unresponsiveness.

B. Experiments with diluted nicotine

When we first injected pure nicotine in the caudal bulbar part that contained the respiratory center, the animal instantly fell into dyspnoea and died soon after. As we had a considerable number of such cases, we turned to using a 1/2 solution of nicotine diluted by a 0.8% methyl cellulose solution which is not stimulative and has adequate viscosity. And the dose of injection was limited to 0.01 cc or less.

1) Pons Groups

Neither the one case (No. 34) which was given injection in the pontine tegmental reticular formation nor the three cases (Nos. 29, 33, 34) which were given injection in the unilateral medial reticular formation at the level between the pons and the rostral bulbar part showed unresponsiveness or any specific movement.

2) Medulla Groups

Of the three cases (Nos. 23, 24, 27), which were given injection in the ventro-medial part of the rostral bulbar reticular formation (nucleus papillioformis), No. 24 (Fig. 11) and No. 27 (Fig. 10) fell into unresponsiveness II and III, the former for three minutes and a half and the latter for about four minutes. No. 22, which was given injection in the dorso-medial reticular formation at the same level showed no unresponsiveness.

The Cat No. 24 (♀, 2.5 kg) ; mews and moves violently before the puncture and the noci-reflex is brisk. It mews loudly and rages when the needle is inserted. The pupils are dilated moderately after injection. Twenty secods later respiration accelerates slightly and mewing and struggling stop. The pupils are contracted, the pupillary reaction to light disappears, and the corneal reflex is weakened. The pharyngeal reflex and the tonus of the muscles are lost and the noci-reflex is nearly lost, too (semi-coma). One minute and fifty seconds later the cat is completely still; the light and the pharyngeal reflexes are elicitable only very little, and the corneal reflex is sluggish. The noci-reflex is entirely lost (coma).

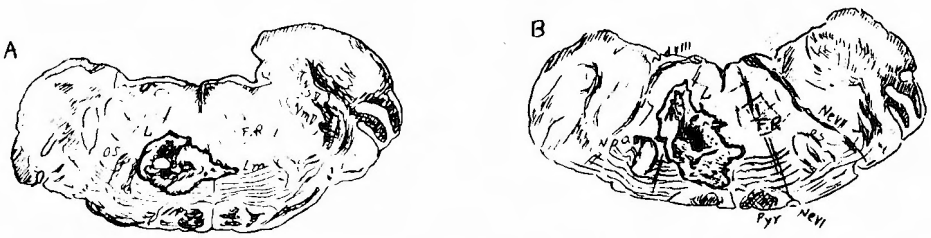


Fig. 10 Transverse sections at the rostral bulbar level (A–B) of No. 27 cat. (coma) Abbreviations are as follows : N. d. Ⅷ; nucleus dorsalis nervi octavi, Ne. Ⅵ. Ⅶ; nervus abducens and facialis, O. s.; nucleus olivaris superior.

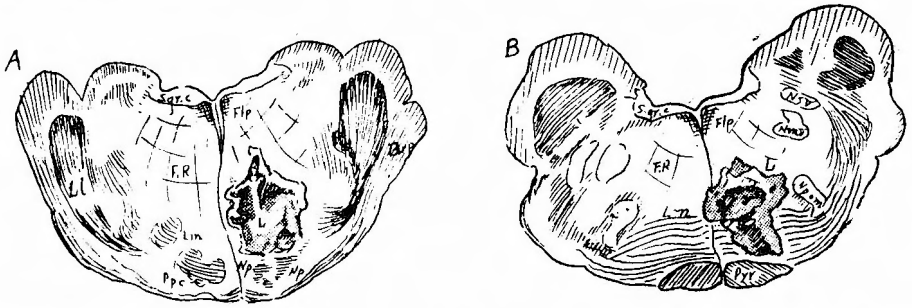


Fig. 11 Transverse sections at the rostral bulbar level (A–B) of No. 24 cat. (coma) Abbreviations are as follows : Br. p.; brachium posticum, F. l. p.; fasciculus longitudinalis posterior, N. p. o. m.; nucleus parolivaris superior medialis, N. m. V, N. s. V; nucleus motorius and sensibiliis nervi trigemini.

Two minutes and twenty seconds later urinary incontinence and the loss of the tonus of the muscles are observed. Three minutes and forty seconds later the tonus of the muscles is recovered and spontaneous movement appears, but no reflex to olfactory stimuli is observable. The pupils are dilated moderately and the light, corneal, and pharyngeal reflexes are all recovered (recovery). Four minutes later the cat vomits and the noci-reflex is almost normal. Five minutes later it mews, shakes its head and licks the chips.

TABLE 1.

Site of Lesion	Cat's No.	Latency up to Coma	Duration of Coma
Midbrain central grey matter	38	25″	10′
	39	30″	4′
Grey masses of the pontine tegmentum	57	1′20″	11′
Nucleus interpeduncularis	41	3′00″	7′
Tegmental reticular formation at rostral bulbar level	46	2′00″	2′30″
Ventro-medial reticularformation at rostral bulbar level (Nucleus papillioformis)	24	20″	3′30″
	27	30″	4′
	74	30″	8′30″
Medial reticular formation at caudal bulbar level	12	30″	4′30″
	14	20″	5′30″
	63	2′00″	3′

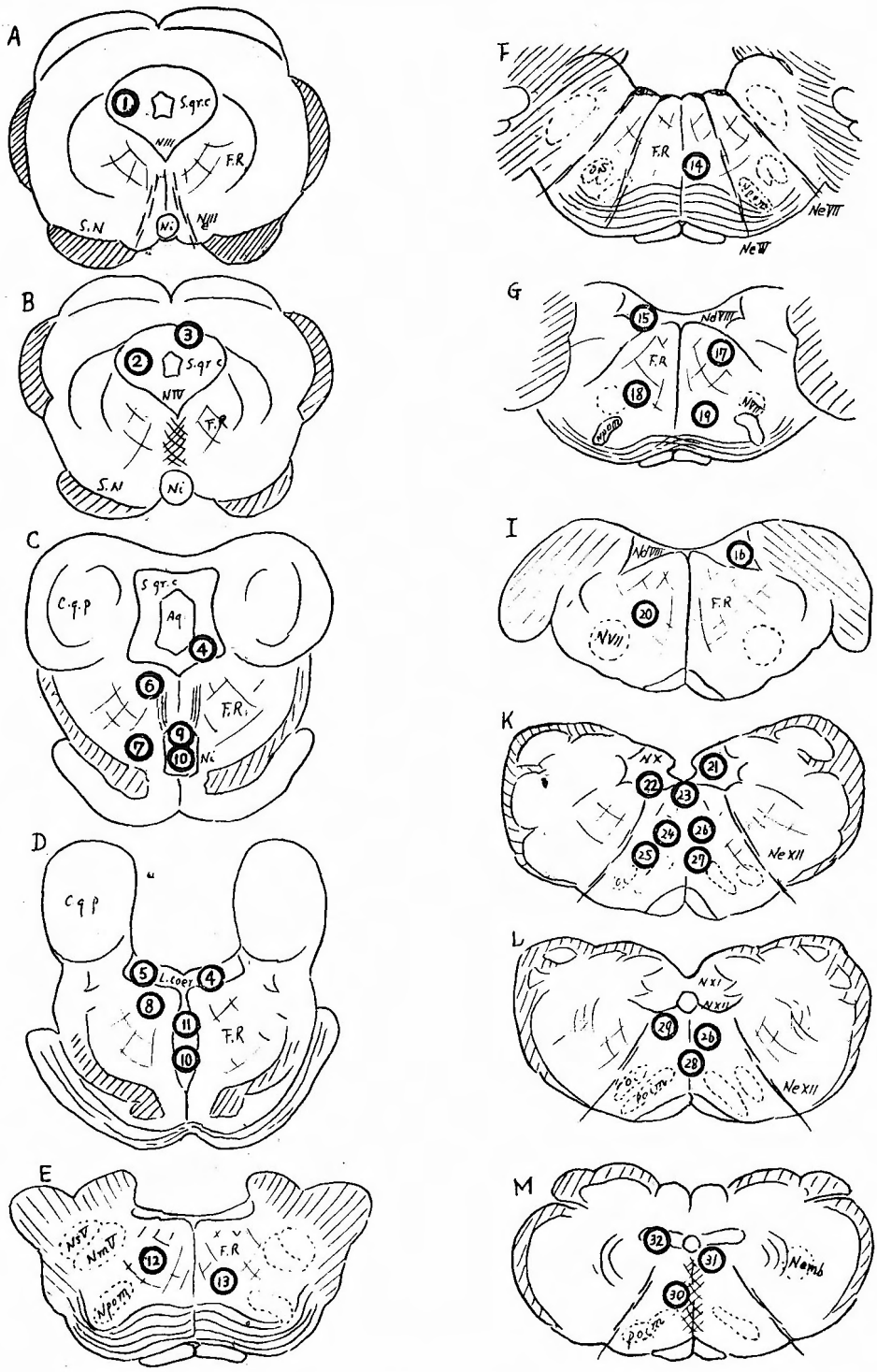


Fig. 12 Diagram of cross sections showing electrically stimulated points.
A-B : midbrain, C-D : pons, E-F : rostral, G-I : intermediate, J-M : caudal bulbar levels.

But unresponsiveness was not evoked at all in the four cases (Nos. 22, 24, 25, 28) which were given injection in the medial reticular formation at the middle part of the medulla, in the two cases (Nos. 25, 26) which were given injection in the floor grey matter, and in the two cases (Nos. 23, 27) which were given injection in the caudal bulbar reticular formation. After all, it follows from this that if diluted nicotine is used death by respiratory paralysis seldom occurs and unresponsiveness also seldom occurs, that is to say, it is not suitable for our experiment.

C. Stimulation experiments with rectangular pulses

In contrast with the nicotine experiments, we examined the changes of responsiveness in 13 cats by giving 1 msec. rectangular pulses directly to about 32 places of the lower brain stem. The stimulated loci are shown in Fig. 12. Stimulatory conditions are 3, 10, 30, 60 and 120 c/s and 1, 2, 4 and 8 volt respectively for each region.

a) Mesencephalic central grey matter: In 1, the noci-reflex has partly and the corneal reflex has totally disappeared with 60 c/s, 4V, but the tonus of muscles is normal. In 2 3, the midriasis and the increased tonus of muscles have appeared with the same condition.

b) Pontine floor grey matter (locus coeruleus): In 4 5, midriasis and the slight general activation are observed with 30 c/s, and over 2V.

c) Pontine reticular formation: In 6 7 8, midriasis and rage with 60 c/s, and over 1V. In 6 8, in the dorsal part, the tonus of muscles has increased. In 8, running movement in the forelegs.

d) Nucleus interpeduncularis: In 9 10, the noci-reflex does not disappear, and the tonus of muscles is strengthened.

e) Raphe nucleus: In 11, no remarkable change occurs.

f) Bulbar reticular formation: In 12···14, 17·· 20, and 23···31, ingeneral, as cycle and voltage increase, the tonus of muscles increases from tremor to rigidity or tonic state, which spreads gradually over the face, the neck, the body, the forelimbs, the hindlimbs till it becomes generalized and is accompanied by activation or rage. In 12···14, in the rostral part, the maximal dilatation of the pupils and the clonic convulsion of the legs occur. In 17···19, in the medial part, midriasis, and in 18 19 running movement is observed. In 23 31, in the causal part, accelerated respiration and vomiting occur in most cases. In the dorso-medial stimulation cases, the face becomes tonic, but the tonus of the legs is normal, while in the ventro-medial stimulation cases, the tonus of the legs is also increased.

g) Nucleus vestibularis: In 15 16, and Nucleus vagus: In 21 22, only the face becomes tonic. The cat opens its eyes and mouth, and rolls its tongue, and the pupils are dilated. In 21 22, rage also is observed.

h) In 32 which has been given stimuli in the caudal bulbar central grey matter shows only the acceleration of the tonus of the muscles.

After all, in the bulbar level stimulations the increase of tonus of the muscles and activation or rage occurred, and unresponsiveness did not occur in all the cases.

Summary

To summarize the above results:···

1) The midsagittal reconstruction of the regions intimately concerned with the nicotine-coma is shown in the Fig. 13, involving the mesencephalic central grey matter, the rostral pontine floor grey matter and the rostral, and the caudal medial bulbar reticular formation.

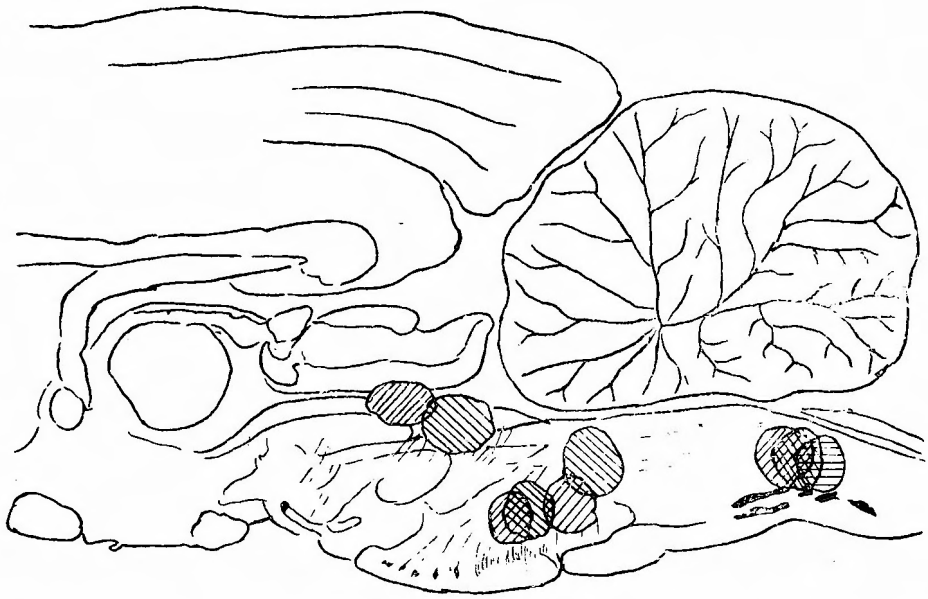


Fig. 13 Midsagittal reconstruction of the lower brain stem showing sites of lesions diagrammatically (shaded areas) in which coma was induced by injection of nicotine.

2) The latency of nicotine-coma and its duration are not characteristic of each region of the brain stem, as in Table I.

3) The changes of the spinal motor activity due to the in jection of nicotine in the brain stem were various ; sometimes the tonus of the muscles, spontaneous movement and escape movement from the noci-stimuli were all nearly normal, while at other times the limbs were flaccid with no motor activity. In the latter case the flaccidity of the unilateral limbs or of the bilateral limbs was seen and the hindlimbs tended to become flaccid sooner than the forelimbs. All the cases of coma showed the flaccidity of the limbs, the disappearance of spontaneous movement, and a remarkable weakening or disappearance of the patellar reflex. The running movement of the limbs was seen when injection was given in the medial reticular formation to the extent from the pons to the middle-third of the medulla, and also at the border between the medulla and cervical cord. The clonic and the tonic convulsions were induced also from much the same region, and also from the lateral bulbar reticular formation of the caudal part of the medulla. And sometimes clonic convulsions changed into running movement. Hence the area where such motor phenomena in the limbs are induced and the region where coma occurs are different in most parts except the rostral bulbar medial reticular

formation. And convulsion and running movement may be assumed to be very closely related to each other.

4) Respiratory paralysis due to the injection of nicotine occurred only in the caudal bulbar reticular formation. This is in accord with the statements of PITTS and MAGOUN. It seems very important that we have been able to separate coma from both respiratory paralysis and convulsion in the present study.

Discussion

From these results it is obvious that the disturbance of consciousness can be evoked by some kind of stimulation in the lower brain stem, i. e. that there is some part in the lower brain stem that has much relation to the maintenance of consciousness. This is not a fact found by us for the first time, but a considerable number of opinions to support it have been reported.

Experimentally, FLOURENS, by puncturing the "LEBENS-KNOTEN" (respiratory center) in the caudal bulbar region, and BRESLAUER (1917), by mechanical pressure on the trans-orally-exposed bulbar base or by arachinoideal haemorrhage of the bulbar base in operative manipulation by mistake, noticed that fulminant unconsciousness occurred suddenly, accompanying respiratory paralysis; and presumed that the chief cause of unconsciousness in commotio cerebri might be in the medulla oblongata. Similar experiments were made by TILANUS, HEUBEL, DEGE, and others. This transient unconsciousness is rather similar to the transient unresponsiveness caused in this experiment by puncturing the floor grey matter of the fourth ventricle (No. 2), or by injecting of nicotine into it (No. 45), or at the sudden thurst of an injection needle upon the skull base. In opposition to BRESLAUER, KNAUER (1922) said that, if the experiment was done taking much care to avoid excessive narcosis, rough operative manipulation and respiratory paralysis, the animal showed only excitation, but never unconsciousness by the pressure which was given either to dorsal or ventral side of the medulla oblongata. As for respiratory paralysis, we succeeded in causing unresponsiveness without accompanying respiratory paralysis.

MAGOUN proved the important relation between consciousness and the brain stem reticular formation, including the bulbar reticular formation. He says that the brain stem reticular formation does ascending background activity to maintain arousal. How should we explain the coma by the injection of nicotine according to his theory? The answer seems to be as follows: The difference between arousal and coma would be the difference in the effects due to the intensity of stimulation. Stimulation usually produces an influence conforming to the pattern of normal nervous excitement inherent in the central nervous system, but an excessive, explosive stimulation like nicotine drives the central nervous system to abnormal excitement or seizure discharge and brings about a depressive paralytic effect of normal function. This is like a general convulsion by an abnormal excitement of the cerebral cortex due to the nicotine locally applied. Examining the nicotine-injected locus histologically, we find a tissue defect in the central part, and the intercellular infiltration of nicotine in the marginal part. Therefore, it is considered

that in such a case a forcible stimulation accompanying destruction was given. But coma in all such cases is short lasting only for about ten minutes. If it is caused by functional loss due to tissue destruction, it must last for a considerably long time. After all, it seems most reasonable to consider that such a coma state originates from paralytic influence caused by a forcible stimulation.

By electrolytic destruction of the central cephalic portion of the mesencephalic tegmentum, LINDSLEY and MAGOUN (1950) in cats, and FRENCH and MAGOUN (1952) in monkeys, respectively, found remarkable behavioral and E. E. G. changes and named the state hypersomnolence or simulating coma. But compared with our unresponsiveness it seems considerably slighter in the grade of the disturbance of consciousness.

BAILEY and DAVIS (1942) succeeded in bringing about a state like CAIRNS' akinetic mutism in cats by a circumscribed electrolytic destruction of the mesencephalic periaqueductal grey matter, a state in which spontaneous activity was completely abolished, only a slight responsiveness being left to a forcible stimulation; and they called that state "arrest of consciousness". They also brought about an apathetical state in a monkey in which the animal showed responsiveness to stimulation but never spontaneous drive and called it "lack of drive." These are also much slighter or weaker in grade than our unresponsiveness.

As important anatomical data in connection with our nicotine-coma is to be regarded the report of BRODAL (1955). He made hemisection at various levels between the mesencephalon and the diencephalon in kittens and examined the retrograde degeneration of cells of the caudal brain stem reticular formation, and found that cellular degeneration was abundant at the level of the rostral third of the inferior olivery nucleus (the caudal bulbar portion) and at the level of the root fiber of nervus abducens (the rostral bulbar portion) and was restricted to the medial two-thirds of the reticular formation at these levels. He said that such retrograde degeneration occurred because the cells had rostral projection beyond the midbrain. It is very interesting that the sites of these degenerated cell groups are equal to the bulbar portion concerned with nicotine-coma in our experiment. Again, according to OLSZEWSKY's cytoarchitectonic atlas of the human brain stem reticular formation (1954) (he says that there is no great difference between man and animals), the remarkable cell aggregates in the two nicotine-coma regions in the bulbar reticular formation correspond to the nucleus centralis pontis, the nucleus papillioformis and nucleus centralis medullae oblongatae, and all these nuclei have not so many large cells, but consist chieffy of small or medium-sized multipolar cells, while in the midbrain, no such remarkable cell aggregate can be seen. From the fact that a distinct difference in the cellular type does exist between the midbrain and the medulla, it may be supposed that there may be some difference in the details of the mechanism of occurrence between nicotine-coma from the midbrain and that from the medullae oblongatae.

The electroencephalogram during coma is generally believed to consist of slow waves, but during our nicotine-coma it was found to consist of low voltage fast waves. This seems apparently strange, but not incomprehensible when we consider

that a forcible stimulation of nicotine may cause coma in behavior and low voltage fast waves in electroencephalogram. So the initial coma in head injury may be analogous. In our laboratory such coma accompanying fast waves was seen in a patient of coma immediately after head injury or in a patient of reticular epilepsy of which ARAKI et al reported elsewhere. WALKER, too, noticed this in experimental commotio cerebri. And LOEB, in a patient of coma owing to the haemorrhage of the tegmentum of the pes pedunculi which perforated into the fourth ventricle, and GASTAUT also, in a patient who had similar perforation into the third ventricle, or in a patient of anoxia owing to an anaesthetic accident, noticed deep coma with a rapid rhythm in E. E. G. and concluded that unconsciousness without accompanying slow waves is sure to exist, though no much attention has been called to it before.

What is the area essential for the maintenance of consciousness is the final end of our study. From the fact that the nicotine-coma from the lower brain stem is lighter in grade, more difficult to induce and shorter in duration than that from the mesencephalic central grey matter, and also from the results of a series of experiments with nicotinization and with electrical stimulation in our laboratory, we are led to believe that the portion which holds the most important control for the maintenance of consciousness is the mesencephalic central grey matter.

Conclusion

1. The regions in the brain stem where coma occurs by the injection of pure nicotine are the mesencephalic central grey matter, the rostral pontine floor grey matter, the rostral and caudal parts of the bulbar medial reticular formation.

2. The latency from the injection of nicotine till the occurrence of coma was from twenty seconds to two minutes. The duration of coma was from three minutes to eleven.

3. Both surface E. E. G. and deep E. E. G. during nicotine-coma showed low voltage fast waves, and neither slow waves nor spindle bursts were seen. And the E. E. G. during this coma did not change at all even by painful stimuli.

4. When rectangular pulse stimulation was given to the same areas, no disturbance in consciousness but activation in behavior occurred.

5. Nicotine-coma did not occur from the mesencephalic and the rostral pontine reticular formation.

6. Nicotine-coma from the lower brain stem was lighter in grade, more difficult to induce and shorter in duration than that from the mesencephalic central grey matter.

7. Judging from these facts, it may be said that it is the mesencephalic central grey matter rather than the medulla that is more important for the maintainance of consciousness.

Thanks are expressed to Dr. Kazuki Sakata for his kind help throughout the experiments.

SECTION II

AN INVESTIGATION ON THE BULBAR AND MESENCEPHALIC INHIBITORY SYSTEM IN UNANAESTHETIZED ANIMALS *

According to MAGOUN, electrical stimulation of the ventromedial part of the caudal bulbar reticular formation inhibits the cortical motor response, the blink reflexes, the flexor reflex of the forelimb, and the patellar reflex of the hindlimb, etc, whereas stimulation of the lateral part of the bulbar reticular formation, the suprabulbar reticular formation, the mesencephalic central grey matter, and the hypothalamus etc, facilitates the cortical motor responses and the patellar reflexes, ··· that is to say, the bulbar reticular formation exerts a descending inhibitory and facilitatory influence on spinal motor activity, whether it is voluntary or reflectic.

In discussing coma (or unresponsiveness) from the medulla oblongata, we must, therefore, consider the following possibilities:···

(1) May the activation of this inhibitory system cause unresponsiveness (the disappearance of the noci-reflex) which we have applied as the criteria of coma?

(2) According to MAGOUN's theory of the ascending reticular activating system, electrical stimulation of the brain stem reticular formation causes E. E. G. desynchronization and behavioral arousal. If it is supposed that there may be an ascending inhibitory system as well as a descending one, though MAGOUN says nothing about it, may it (the ascending inhibitory system) not be responsible for disturbance of consciousness?

(3) And again, may there not be a descending or ascending inhibitory influence from the mesencephalic central grey matter, which we have regarded as being important in relation to consciousness?

The aim of the present experiment is to examine these three points.

Methods

In cats 1.5 to 2 kg in weight, anaesthetized moderately so as to nearly lose their spontaneous movement by intramuscular injections of divided doses of barbituate (Isomital), cortical motor responses were induced by stimulating the exposed motor cortex regularly at two-second intervals by means of rectangular pulses of 4.4 to 6 msec. duration at 20 to 24 volts, and the responses of the contralateral forelimb and hindlimb were recorded on a kymograph. For inducing the patellar reflexes cats were placed in the dorsal position with fixation of the spinal process and the femoral bone, and the patellar tendon was tapped with constant power regularly at 4 seconds intervals by JOHNSON's apparatus and the resulting reflexes were recorded on a kymograph. The brain stem was stimulated on the same side as that of the motor responses to be recorded, by employing 60 cycle, sine wave current, at 0.5 to 8 volts, through the bipolar electrode being oriented with the HORSLEY-CLARKE technique. And while the cortical motor responses and the patellar reflexes were being inhibited by the brain stem stimulation, the

* Read at the Sixth General Meeting of the Japan E. E. G. Society in Sapporo on July 3, 1957.

noci-stimuli were given and the responses were macroscopically observed.

And in addition we examined how spontaneous E. E. G. and the electromyogram of various skelet muscles (flexor and extensor muscles of limbs, neck muscles, masseter muscles and respiratory muscles) were influenced at the time of descending inhibition. In order to keep away artifacts from the records, 150 to 200 cycle rectangular pulses at 1 msec. duration were employed for the brain stem stimulation, and under this experimentary condition, descending inhibition was likewise observed. In each animal, the stimulated points of the brain stem were affirmed histologically in serial sections by NISSLE stain and iron-carmin stain.

Results

1) Bulbar inhibition of the cortical motor response and the patellar reflex, and the disappearance of responsiveness to noci-stimuli during the inhibition.

The stimulation of the medial part of the bulbar reticular formation was found to inhibit the cortical motor response in the forelimb and the hindlimb and the patellar reflex. As shown in Fig. 14. B, cortical motor responses disappeared completely during stimulation by 60 cycle, sine wave current at 4 volt (i. e. during the period marked by the signal), and after the cessation of stimuli the response augmented on rebound, owing to the release from inhibition. The reduction of the tonus of the limbs by bulbar stimulation in this case is shown in C. As soon as stimulation set in, the tremor of the limbs stopped and the tonus was gradually reduced, and after the cessation of stimuli the reduction of the tonus became more remarkable for a time and then rapidly recovered.

Inhibition of the patellar reflex is shown in E.

Sixty cycle, sine wave current at 1 volt caused a complete inhibition of the patellar reflex. 60 cycle, rectangular pulses at 1 msec. 1 volt caused an in complete inhibition, the patellar reflex sometimes appearing during the inhibition. During such bulbar inhibition, the tonus of the limbs was reduced, and respiration stopped.

TABLE 2. Changes of Responsiveness to Noci-Stimuli during Bulbar Inhibition of Cortical Motor Responses & Patellar Reflexes.

Case No.	1		2		3		4		5	
Bulbar Stimulation / Items of Examinations of Responsiveness	Before	During	Before	During	Before	During	Before	During	Before	During
Spontaneous Movement	+	−	+	−	+	−	−	−	−	−
Responsiveness to olfactory Stimui	+	−	±	−	±	−	−	−	−	−
Responsiveness to Painfull Stimuli to Ear	±	+	±	+	+	−	+	−	±	−
Responsiveness to Painfull Stimuli to Nose	±	+	±	+	+	−	+	−	±	−
Responsiveness to Painfull Stimuli to Nasal Septum	±	+	±	−	+	−	+	−	−	−
Responsiveness to Painfull Stimuli to Extremity	±	+	±	−	±	−	+	+	+	−
Corneal Reflex	±	+	±	+	+	−	+	−	−	−
Pharyngeal Reflex	±	−	+	−	±	−	+	−	+	−
Tonus of Muscles	+	−	+	−	+	−	+	−	+	−
Respiratory Movement	+	−	+	(+) −	+	−	+	−	+	(+) −

And responsivenesses to the noci-stimuli were nearly extinguished, but some of them were still remaining (Table 2).

And bulbar inhibition is demonstrable even in deep anaesthesia, and persists so long as cortical motor responses or reflex activities are demonstrable.

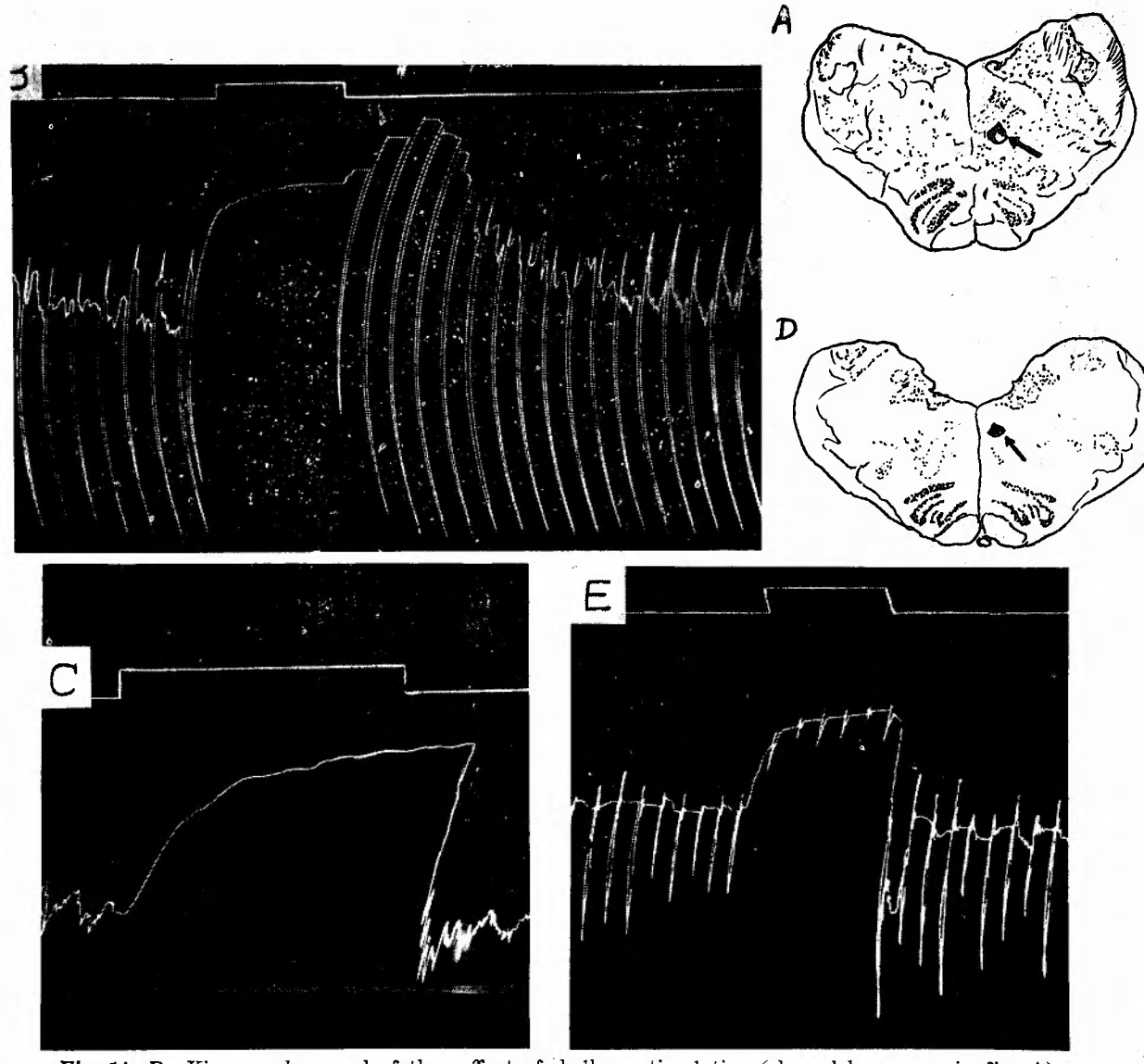


Fig. 14 B : Kimograph record of the effect of bulbar stimulation (showed by arrow in fig. A) on the cortical motor responses. C : Reduction in muscle tonus evoked by the same stimulus. E : Kimograph record of the effect of bulbar stimulation (showed by arrow in fig. D) on the patellar reflexes.

2) Mesencephalic (central grey matter) inhibition of the cortical motor response and the patellar reflex, and the disappearance of responsiveness to noci-stimuli during the inhibition.

The cortical motor response of the hindlimb, caused in the same way as in

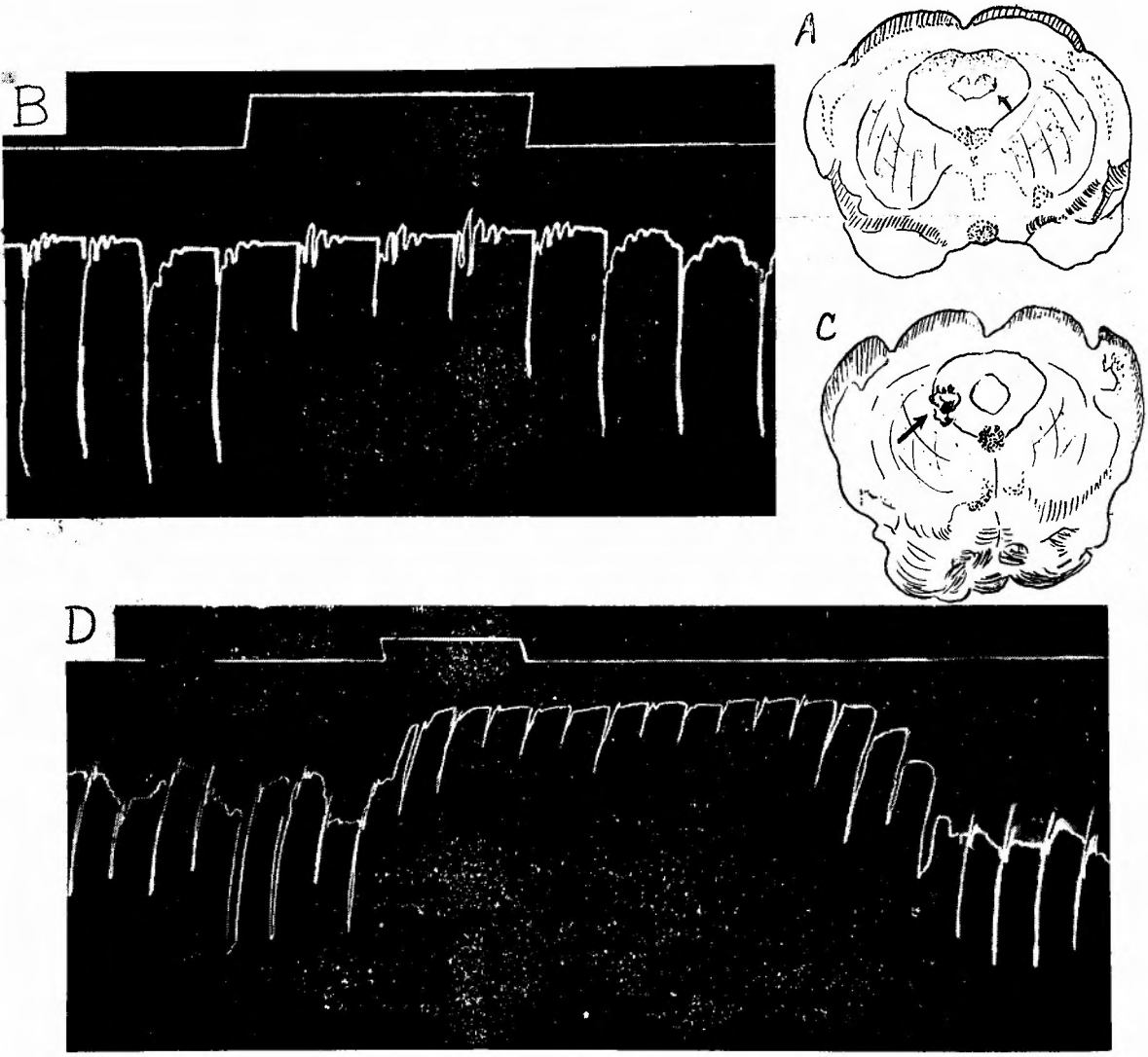


Fig. 15 B: Kimograph records of the effect ofmidbrain central grey matter stimulation (showed by arrow in fig. A) on the cortical motor responses. D: Kimograph records of the same stimulation (arrow in fig. C) on the patellar reflexes.

the previous experiment, was remarkably reduced when stimulation was given to mesencephalic central grey with 60 cycle, sine wave current at 4 volts, as is shown in Fig. 15. B. What differed from the bulbar inhibition was that inhibition was incomplete and accompanied no rebound augmentation of responses after the cessation of stimuli. Inhibition of the patellar response under the same condition is shown in D. As soon as stimulation set in, the tonus of the limbs was reduced, and the patellar reflex was remarkably diminished. This inhibitory influence continued long after the cessation of stimuli and was gradually lost.

Responsiveness to noci-stimuli was found to disappear almost completely during inhibition from the mesencephalic central grey matter (Table 3).

TABLE 3. Changes of Responsiveness to Noci-Stimuli during Mesencephalic Inhibition of Cortical Motor Responses & Patellar Reflexes

Case No.	1		2	
Items of Examinations of Responsiveness / Mesencephalic Stimulation	Before	During	Before	During
Spontaneous Movement	+	−	−	−
Responsiveness to Olfactory Stimuli	+	−	+	−
Responsiveness to Painfull Stimuli to Ear	±	+	+	−
Responsiveness to Painfull Stimuli to Nose	±	−	+	−
Responsiveness to Painfull Stimuli to Nasal Septum	+	−	+	−
Responsiveness to Painfull Stimuli to Extremity	±	−	+	−
Corneal Reflex	±	−	+	−
Pharyngeal Reflex	−	−	+	−
Tonus of Muscles	+	−	+	−
Respiratory Movement	+	−	+	−

On the other hand, when stimulation was given under much the same condition to the mesencephalic and pontine reticular formation, the cortical motor response or the patellar reflex was rather facilitated.

Such descending inhibition from the bulbar reticular formation and mesencephalic central grey matter and decrease or disappearance of responsiveness to noci-stimuli during the inhibition were observed in animals under moderate anaesthesia. The unresponsiveness (the loss of noci-stimuli) that we have so far adopted as the criteria of coma in our experiment was the one in unanaesthetized animals, so simular observation must be done in unanaesthetized animals.

3) Changes of the influence of stimulation of the bulbar reticular formation on the cortical motor response at various stages of anaesthesia.

In case of electrical stimulation of the bulbar inhibitory area in unanaesthetized animals, as already mentioned in the experiment by electrical stimulation in Section I, we could see no tendency to unresponsiveness or inhibition but the increased muscle tonus and behavioral activation or rage. Now, the effect of stimulation given to a certain point in the bulbar inhibitiory area, on the cortical motor response was observed at various stages of gradually deepening anaesthesia. In unanaesthetized state or in light stage of Isomital anaesthesia in which some spontaneous movement still remained, we could observe, on stimulating this point, a generalized tonic reaction of the whole body, the flexion of the limbs, struggling, and behavioral rage. In the stage in which spontaneous movement disappeared but the tonus of the muscles was still kept practically normally, the bulbar stimulation caused a tonic flexion of the limbs and activated the animal in behaviour, as is shown in Fig. 16. A. And as in Fig. 16. B, as anaesthesia a little more deepened and the tonus of the muscles was somewhat reduced, the cortical motor responses augmented during the bulbar stimulation, though the tonus of the muscles was strengthened and became rigid temporarily the initial stadium of stimulation; and as stimulation continued the tonus of the muscles got further strengthened

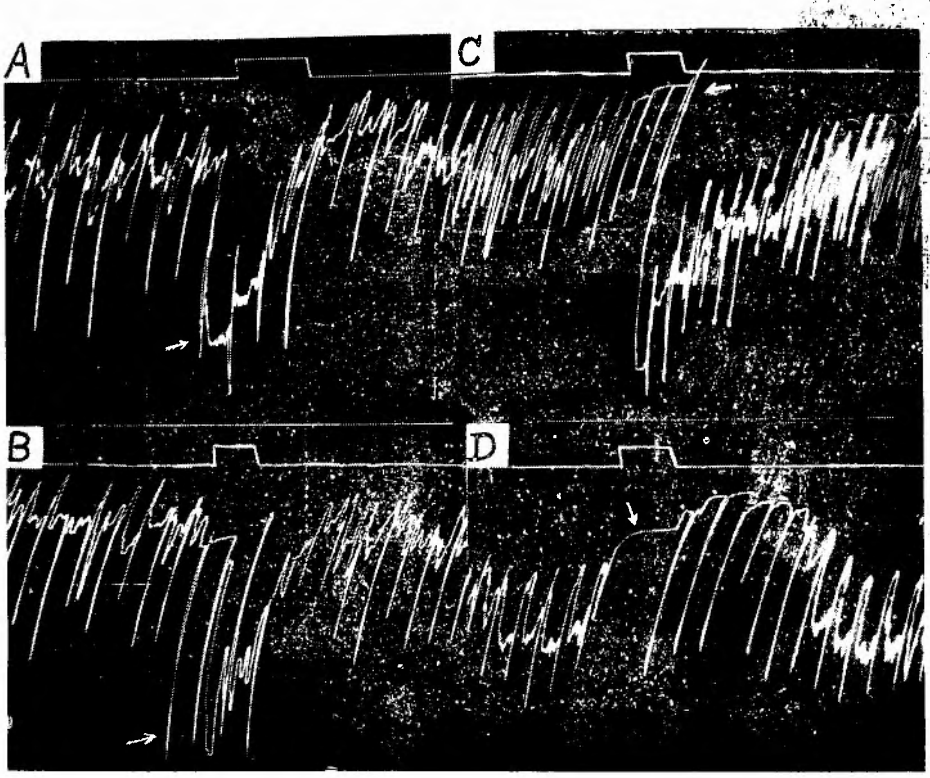


Fig. 16 Changes of the effect of the same bulbar stimulation on the cortical motor responses in various anaesthetic conditions. A : Tonic flexion of legs in light anaesthesia.(←—) B : Facilitation of c. m. r. in moderate anasthesia.(←—) C : Reduction in tonus during stimulation. (←—) D : Inhibition of c. m. r. in deep anaesthesia. (←—)

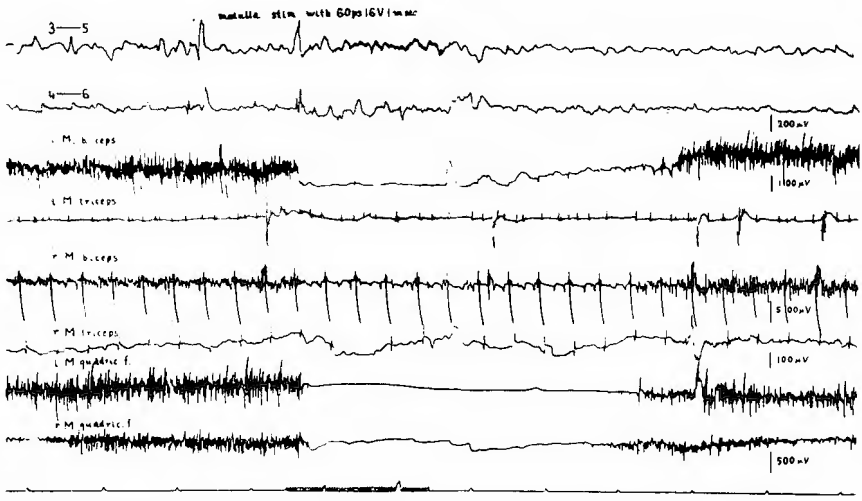
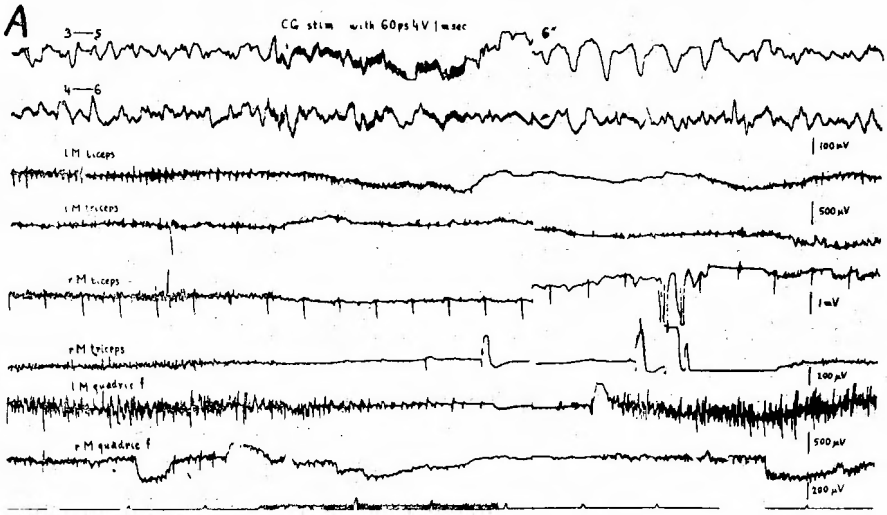


Fig. 17 Shows the EMG changes (lower six beams) led from antagonistic muscles on both sides evoked by the bulbar stimulation (during the period marked by the signal in the lowest beam).

and reponses were weakened; and instantly after the cessation of stimuli the tonus of the muscles was strengthened to an extreme degree and then gradually restored



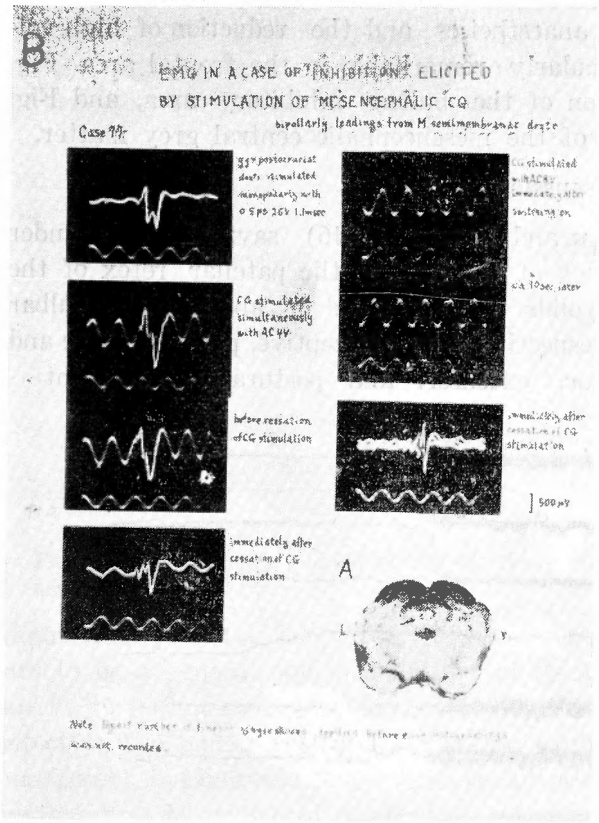


Fig. 18 A : EMG changes (lower six beams) elicited by the electrical stimulation of mesencephalic ccentral grey matter. B : Oscillographical recordings of the same effect.

to the prestimulatory state. At the next stage following this period of light anaesthesia facilitation (B), as anaesthesia deepened, the tonus of the muscles was weakened as soon as stimulation began as in (C), while the response itself showed neither facilitation nor inhibition, and then limbs became extremely flaccid instantly after the cessation of stimuli, and at the next moment showed tonic flexion and then gradually restored (C). Inhibitory effect did not appear till anaesthesia further deepened to a stage, when the tonus of the muscles was more reduced, and the limbs had become flaccid (D). At this stage, facilitation of cortical motor responses was observed as a rebound phenomenon after the cessation of stimuli.

In short, descending inhibition did not occur by a mere stimulation of the inhibitory area, without moderate anaesthesia. Thus unresponsiveness (coma) in

unanaesthetized animals, with which we have dealt before, should be different from unresponsiveness due to such descending inhibition.

4) E. M. G. under inhibitory influences

During such descending inhibition, E. M. G. s were recorded from various skelet muscles (neck, chew, intercostal and flexor and deflexor muscles, etc.). Not only during bulbar inhibition as in Fig. 17, but also during mesencephalic inhibition as in Fig. 18, waves in E. M. G. disappeared. The stoppage of waves occurred bilaterally, and in both antagonistic muscles simultaneously; that is to say, it was a non-reciprocal, and geneneralized stoppage covering all the limb muscles and the intercostal muscles and the others, and often showed a rebound phenomenon after the cessation of stimuli.

5) E. E. G. under inhibitory influences

Changes of electrocorticogram recorded from the six points, namely both an anterior and a posterior pole on either side and each two points of the right and the left side of the cerebral cortex, during obvious descending inhibition, showed a complete stoppage of burst activity by anaesthetics and the reduction of high voltage waves. Such changes were particularly remarkable in the frontal area. Fig. 19 shows changes during the stimulation of the bulbar inhibitory area, and Fig. 20 shows those during the stimulation of the mesencephalic central grey matter.

Discussion

In their inhibition theory, MAGOUN and RHINES (1946) say; "In cats under chlorolosane anaesthesia, the flexor reflex of the foreleg, the patellar refex of the hindleg and the blink reflex of the eyelids were reduced or abolished by bulbar stimulation. These reflexes, initiated respectively by nociceptive, proprioceptive and tactile stimuli, involve muscles ··· flexor, extensor, and posturally indifferent ···

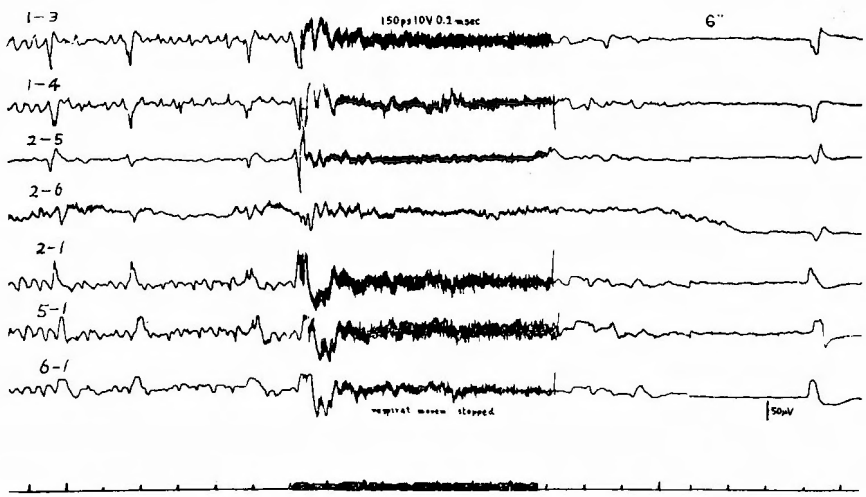


Fig. 19 EEG changes elicited by the bulbar electrical stimulation during the period marked by the signal in the lowest beam. EEG tracings were led from midline frontal (1) and occipital (2) ends of cerebral convexity, left (3) and right (4) coronarius gyrus and left (5) and right (6) posterius ectosylvius gyrus.

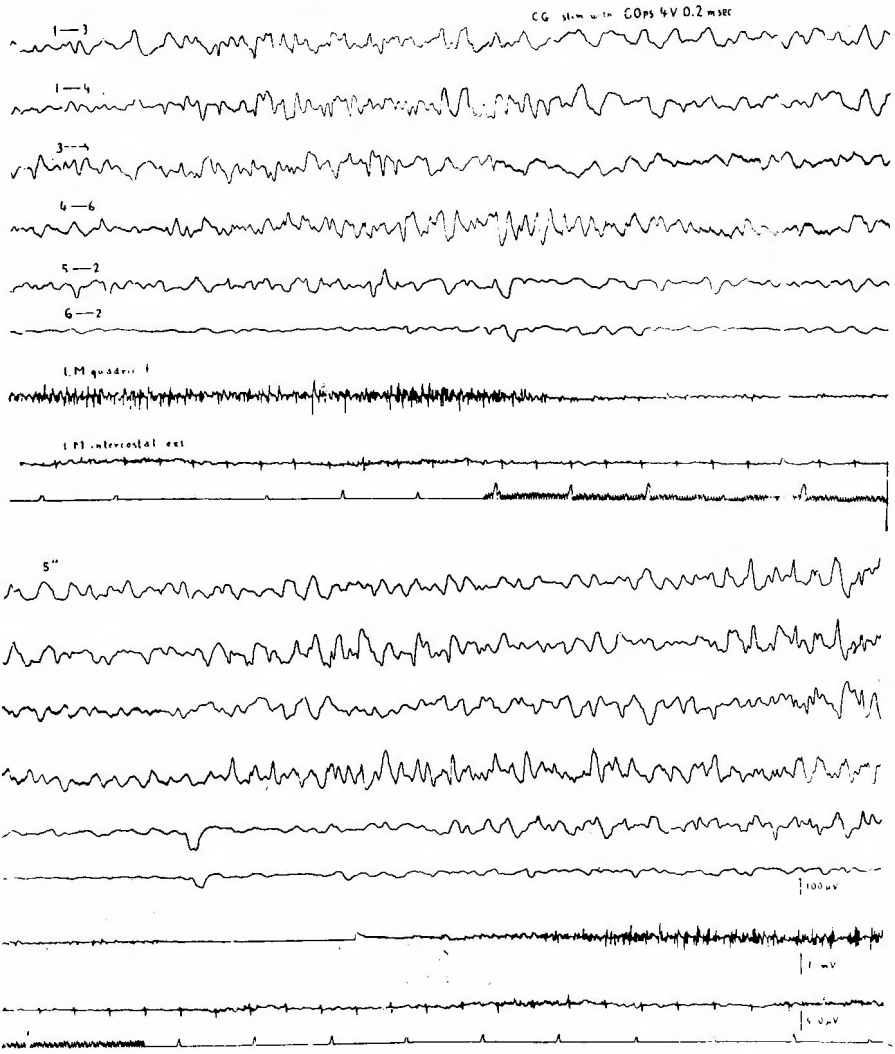


Fig. 20 EEG changes elicited by the electrical stimulation of the mesencephalic central grey matter.

distributed over the length of the body. The bulbar inhibitory influence thus appears to be a general one, not limited in its action to functionally specific or topographically circumscribed reflex acts." And they go on to say that such inhibitory effect of the bulbar reticular formation upon reflex activity and cortically induced movement is bilateral but more remarkably ipsilateral; that after inhibition the augmenting of responses is often observed as a rebound phenomenon as a result of release from inhibition; and that the site of inhibition here is evidently spinal rather than cortical. If such generalized inhibition of reflex activity and cortically induced movement should occur, the resulting state may be supposed to be similar to the unresponsiveness which we have been considering. But according to our experience unresponsiveness due to such an inhibition is not so complete as that which we have been using as criteria of coma. Besides, we must not forget that

the above-said experiments on inhibition were all in anaestheized animals. The coma at the time of head injury and also our experimental coma were all under unanaesthetized state, so we must again examine whether inhibition can really occur or not in unanaesthetized animals. And as already said in the rectangular pulse stimulation experiment in Section I of this study, the stimulation of the bulbar inhibitory area in unanaesthetized animals resulted in only generalized activation or rage, which was different far from inhibition. We cannot find any such experiment of inhibition in references. So, in order to make the matter clear to understand, we made an experiment to examine the changes of the effect of stimulation of the bulbar inhibitory area in various stages of anaesthesia, and found that only generalized activation and exaggeration of motor activity or tonic flexion of the limbs occurred in unanaesthetized animals. And inhibition occurred only in the fairly deep anaesthetized state, while in the light stage of anaesthesia temporary facilitation was observed. Accordingly, generalized inhibition is a phenomenon occurring only under specific condition of anaesthesia. It is not right to consider that the bulbar reticular formation has a facilitatory and inhibitory influence on spinal motor activity under ususal physiological condition. Generalized inhibition under anesthesia is different from the coma (unresponsiveness) which we have observed under unanaesthetized condition. To regard our unresponsiveness as a state influenced by central inhibition in the sense of MAGOUN's is not assuring. SPRAGUE et CHAMBERS (1954), too, say that inhibitory influence does not occur under unanesthetized condition. When they gave electrical stimulation to the medial or lateral bulbar reticular formation in unanaesthetized animals they could observe only specific movement; and under light Nembutal anaesthesia, in most cases, reciprocal inhibition or facilitation of the postural tonus was observed; and a change from reciprocal inhibition to generalized inhibition was very rarely found; and a generalized inhibition, if occurred, was found to originate from both medial and lateral bulbar reticular formation. They say in conclusion, "The concept of generalized, diffuse, non-reciprocal 'inhibitory' and 'facilitatory' functions of the reticular formation is valid only within rather limited experimental conditions." In our opinion 'limited experimental conditions' may mean 'adequate anaesthetic depth', for according to our findings, generalized inhibition is pretty easy to occur under fairly deep anaesthesia. And the inhibitory area is not limited to the ventro-medial part of the bulbar reticular formation but is also near the dorso-medial part, i. e. fasciculus longitudinals posterior. And the inhibition we got under deep anaesthesia was a generalized one, as is obvious from the electromyographical tracings.

And the descending facilitatory area referred to by RHINES and MAGOUN (1946) includes the ascending reticular activating system except the medial bulbar reticular formation ··· namely, the lateral bulbar reticular formation, the pontine and mesencephalic reticular formation, the sub-and hypothalamus and some thalamic nuclei, etc. ··· and even the mesencephalic central grey matter, believe it or not. We have so far regarded the mesencephalic central grey matter as the part in

the brain stem most likely to bring about disturbances of consciousness by various stimulatory methods. Does similar inhibition not occur from the mesencephalic central grey matter as well as from the bulbar reticular formation? We have examined about it, and found that much the same inhibition occurs, though not so remarkable as the one from the medulla. And further, we have found that inhibition from the mesencephalic central grey matter is bilateral, and does not accompany any facilitatory rebound phenomenon after inhibition, and all the responsiveness to noci-stimuli disappears just as the unresponsiveness of our former nicotine study. But even in this case it must be remembered that the inhibitory phenomenon is still the one under deep anaesthesia.

As for descending facilitatory influences, by the way, aside from light anaesthesia facilitation from the medial bulbar reticular formation, definite facilitation occurs from the lateral bulbar reticular formation and the mesencephalic and the pontine reticular formation. Also in the latter case, under light anaesthesia, stimulation causes the tonic flexion of the limbs and only under deep anaesthesia it causes typical facilitation, which never changes into inhibition, however deep anaesthesia may be. To summarize, we will show the results in the following table.

depth of anaesthesia / stimulation area	nonanaesthesia or light anaesthesia ⟶ moderate anaesthesia⟶deep anaesthesia
stimulation of inhibitory area	tonic flexion⟶temporary facilitation⟶inhibition
stimulation of facilitatory area	tonic flexion⟶facilitation⟶loss of facilitatory effect

And it seems that the inhibitory and the facilitatory area cannot be so clearly separated in certain regions as Magoun and other say, but even the remove of the stimulation point for 1 mm dorsal, or ventral, or medial, or lateral may cause the disappearance of inhibitory effect.

The changes that the stimulation causing descending inhibitory influence brings on E. E. G. was found to be considerably remarkable at the stimulation of both the mesencephalic central grey matter and the bulbar reticular formation, but we dare not say that this is an ascending inhibitory influence to cerebral function.

Conclusion

1) In Isomital anaesthetized cats, the noci-stimuli, given during the inhibition of the cortical motor response and the patellar reflex by the stimulation of the bulbar inhibitory area, fail to induce most of the various noci-reflexes.

2) In unanaesthetized animals, the electrical stimulation of the inhibitory bulbar reticular formation activates the animals, and all the motor activities are exaggerated. Under anaesthesia, as it deepens, a change through temporary facilitation of the motor response into inhibition is seen.

3) The same inhibitory influence under anaesthesia is gained also from the

mesencephalic central grey matter, but it is not so complete as from the medulla oblongata. But in this case, the noci-reflex disappears completely during inhibition.

4) During descending inhibition, the E. M. G. pattern of the skelet muscles (involving the respiratory muscles) in various parts of the body disappear.

5) The changes of E. E. G. during descending inhibition are a complete disappearance of burst activity and a remarkable change of spontaneous E. E. G. in the frontal region.

6) Consequently we cannot regard in the same light the state under descending inhibition as the unresponsiveness (coma) that have so far been seen in our previous experiments, the former being the state under anaesthesia, and the latter a phenomenon under nonanaesthesia.

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和文抄録

下部脳幹と意識障碍

京都大学医学部外科学教室第1講座（指導：荒木千里教授）

守安久

下部脳幹と意識障害との関係を追究する目的で次の実験を行つた．

i) 下部脳幹の一定の部分をねらつてニコチンの微量注射をすると，中脳では中心灰白質，橋脳では吻端部第四脳室底灰白質，延髄では吻端部被蓋網様織と尾端部の内網様織から昏睡（無反応）が起つた．従つてこれらの部分は意識の維持に深く関与している部分と思われる．

ii) ニコチン昏睡中の脳波は表面，深部脳波とも低電位速波で覚醒時と殆ど変りがない．即ちニコチン昏睡は behavior 上では昏睡を脳波上ではarousal pattern を示す．

iii) 対照実験として略同じ部分を直接矩形波電流で刺戟すると，意識障害は起らず behavior 上の activation を示す．

次で延髄抑制系（延髄尾端部内網様織）の刺激によつて起る generalized inhibition（Magoun）と吾々の無反応とを対比吟味する意味で次の実験を行つた．

i) Magoun に倣つて麻酔猫で，脊髄運動性が延髄内側網様織刺激によつて下行性に抑制されている間に，侵害刺激を加えるとそれに対する諸反応は一部を除き大部分が消失する．

ii) 無麻酔猫で同様の実験を行うと，抑制は起らず逆に activate され運動現象はすべて亢進する．麻酔を加えると，麻酔が深くなるにつれて一過性の運動反応の促進期を経て抑制期えと移行する．従つてMagoun の generalized inhibition と吾々の無反応とは麻酔という条件の異いがあるために同一に論ずるわけにゆかない．

iii) 同様の麻酔下抑制は中脳中心灰白質の刺激によつても起るが，延髄性ほど完全ではない．然し中脳性抑制中は侵害反応は全く消失する．

iv) 下行性抑制中は諸種の筋電図波形は停止し，脳波では burst activity の完全な停止と，前頭部に著明な自発脳波の変化がみられる．